REMARKS

This Amendment, filed in reply to the Office Action dated February 8, 2008, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 18-35 are all the claims pending in the application. Claims 18-35 are rejected. Claims 27-29 and 32-34 are amended herewith solely to improve clarity. Support for these amendments can be found throughout the specification, and is inherent in the examples in Applicants' specification as originally filed. No new matter is added by way of this amendment. Entry and consideration of this amendment are respectfully requested.

Information Disclosure Statement

In paragraph 6, on page 3 of the Office Action, the Examiner states that the Information Disclosure Statement filed October 29, 2007, does not comply with the requirements since only an Abstract of the Fujioka *et al.* reference was provided.

In response, Applicants note that in the Information Disclosure Statement Letter filed October 29, 2007, Applicants inadvertently stated that document cited on the PTO Form SB/08 was submitted in the parent application, namely U.S. Application No. 10/429,003, when only the abstract was submitted. Accordingly, Applicants attach herewith a revised PTO Form SB/08 correctly citing the document submitted in the parent case. Applicants respectfully submit that the revised PTO Form SB/08 is fully compliant with the requirements of 37 CFR 1.98.

Claims 27-35 are Definite Under 35 U.S.C. § 112, Second Paragraph

In paragraph 9, on page 3 of the Office Action, Claims 27-35 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

1. With specific regard to Claim 27, the Examiner asserts that it is unclear in part (b) if the expression "specific for said breast cancer" refers to the recitation of "breast cancer" in the preamble or part (a) of the claim, or to recitation of the "very early breast cancer," as recited in part (b) of the claim. Claims 28 and 29 are rejected on the same ground.

Whilst Applicants respectfully submit that one of skill in the art would understand that recitation of "specific for said breast cancer" refers to the recitation of breast cancer in part (a) or the preamble of the claim, solely to advance prosecution, Applicants herewith amend Claims 27-29 to even further clarify that "said breast cancer" refers to the recitation of "breast cancer" in the preamble, or part (a) of the claim by making recitation of "very early stage breast cancer" the final reference to breast cancer in the claims. Applicants respectfully submit that the amendments overcome this aspect of the rejection.

2. With specific regard to Claim 32, the Examiner states that the expression "said isolated cDNA" is confusing, as it is not clear whether Claim 32 requires that any one of the isolated cDNA are labeled, or all are labeled. Further, the Examiner states that this claim is only limiting in the case where the method is performed to produce isolated cDNA, yet all of the claims from which Claim 32 depends recite the step of producing isolated cDNA in the alternative.

Solely to advance prosecution, and without acquiescing in the rejection, Applicants herewith amend Claim 32 to recite that "wherein when isolated cDNA is obtained, any of said

isolated cDNA is labeled." Applicants respectfully submit that the amendment overcomes this aspect of the rejection.

Withdrawal of the rejection is respectfully requested.

Claims 27-35 are Adequately Described Under 35 U.S.C. § 112, First Paragraph

On page 2 of the Office Action, the Examiner indicates that the rejection for lack of written description is maintained.

Specifically, the Examiner states that practicing the method of Claims 27-29 requires hybridization of a particular set of probes that are identified only by their function, i.e., differentially present in two samples (and that are indicative of cancer) and by the type of cells that they were identified within (blood cells) that have not touched the area of disease and which were isolated distant from the area of disease.

Without agreeing with the rejection, and solely to advance prosecution, Applicants herewith amend Claims 27-29 to incorporate the subject matter of Claim 18, which recites the steps of isolating the 10 or more mRNA or cDNA species useful for diagnosing or identifying breast cancer. Applicants respectfully submit that the introduction of these additional method steps into Claims 27-29 obviates the rejection, as the process for obtaining these mRNA or cDNA species is fully described. Further, Applicants note that Claim 18 was not previously rejected for lacking an adequate written description.

Withdrawal of the rejection is respectfully requested.

Claims 18-35 are Patentable Under 35 U.S.C. § 103

1. In paragraph 17, on page 5 of the Office Action, Claims 18 and 20-25 are rejected under 35 U.S.C. §103 as being unpatentable over Ralph *et al.* in view of Lukas *et al.*

The Examiner asserts that Ralph *et al.* disclose a method for cancer detection and diagnosis by detecting a response of circulating leukocytes to the disease state, including the steps of amplifying human peripheral blood mRNAs from healthy and diseased individuals and selecting mRNAs that are differentially expressed between normal and diseased individuals. The Examiner also asserts that Ralph *et al.* disclose separation of the amplification products, and the step of converting RNAs into cDNAs.

However, in setting forth the rejection, the Examiner acknowledges that Ralph *et al.* do not teach a method wherein the cancer is very early stage breast cancer. In an attempt to rectify this deficiency, the Examiner cites to Lukas *et al.*, who allegedly disclose differential display analysis in order to identify genes which are differentially expressed in breast ductal carcinoma *in situ* (DCIS) relative to invasive breast carcinoma, and identified 119 mRNA species which are differentially expressed. From the above references, the Examiner concludes that it would have been obvious to modify the method of Ralph *et al.*, so as to apply such to the study and diagnosis of DCIS as taught by Lukas *et al.* to achieve the present invention.

Applicants respectfully disagree, and traverse the rejection on the following grounds.

Applicants respectfully submit that one of ordinary skill in the art would not reasonably combine the teachings of Lukas *et al.* and Ralph *et al.*, for the following reasons.

First, Applicants' claimed invention is directed to noninvasive techniques for cancer diagnosis, in which tumor cells are not directly examined, but rather, non-tumor cells isolated from blood are examined and used diagnostically. Thus, Applicants' claimed method does not

require identification and purification of tumor cells to make a diagnosis. In this regard, Lukas *et al.* is entirely silent as to whether blood cells in a patient with DCIS would exhibit modified expression, let alone whether such expression could be used diagnostically. At best, Lukas *et al.* disclose that the disease (tumor) cells themselves exhibit altered expression, which is entirely irrelevant to a finding of obviousness of the claimed invention. Neither the cited references nor the art itself teaches or even reasonably suggests that very early stage breast cancer could be detected or diagnosed by examining non-tumor cells from the blood of patients with such cancer. Accordingly, Applicants respectfully submit that one of ordinary skill in the art would not have possessed any motivation, nor any expectation of success in combining Lukas *et al.* and Ralph *et al.*, for at least this reason.

Applicants also note that Lukas *et al.* only discloses results from a single patient appearing to suffer from benign epithelial hyperplasia, breast ductal carcinoma and invasive breast carcinoma. See lines 11-13. Further, at no point do Lukas *et al.* compare the findings from this single patient, exhibiting 3 different tumor types, to *any* control patients to validate or normalize their results. Accordingly, Applicants respectfully submit that one of ordinary skill in the art would not be motivated to combine Lukas *et al.* and Ralph *et al.*, and would not possess any expectation of success in making such a combination, as the results of Lukas *et al.* would clearly be viewed as lacking in scientific merit. Further still, as the single patient was afflicated with multiple distinct cancers, one of ordinary skill in the art would have no understanding whatsoever of which markers would correlate to which disease state if blood cells were analyzed. Further, it is entirely possible that the results observed in the single patient observed by Lukas *et al.* are not representative of the DCIS disease state, and that the multiple different tumors in this patient may affect the differential expression observed in each other tumor. One of ordinary skill

in the art would have no way of discerning from Lukas *et al.* whether DCIS produces any differential expression in non-tumor cells in the blood, and thus would not rely on Lukas *et al.* for the purpose claimed by the Examiner. Even in relation to the results observed in tissues, the disclosure of Lukas *et al.* fails to provide even a suggestion that DCIS could be diagnosed by the use of differential expression analysis.

Accordingly, one of ordinary skill in the art would have no expectation of success in combining Lukas *et al.* and Ralph *et al.* It is respectfully submitted that one of ordinary skill in the medical and biotechnological arts would not reasonably consider combining Lukas *et al.* and Ralph *et al.* when in fact neither Lukas *et al.*, Ralph *et al.*, nor the art itself, reasonably suggests that DCIS results in differential expression patterns in non-tumor blood cells. The rejection is firmly grounded in impermissible hindsight reasoning using data gleaned from Applicants' disclosure.

In addition to the above points, Applicants respectfully submit that the claims are not rendered obvious by Lukas *et al.* and Ralph *et al.* at least in view of the following. Specifically, as mentioned above, Lukas *et al.* do not even suggest that DCIS could be diagnosed on the basis of a blood sample. Further, the method of Ralph *et al.* would not reasonably be considered by one of ordinary skill in the art to be applicable to very early stage breast cancer, such as DCIS, and therefore one of ordinary skill in the art would not possess any motivation to combine Lukas *et al.* and Ralph *et al.*, absent information that DCIS can be diagnosed by analysis of differential expression patterns of non-tumor blood cells. Specifically, at best, Ralph *et al.* compares gene expression levels in blood samples from patients with metastatic prostate or breast cancer to those in normal blood samples by non-sequence based methods and identified genes that showed differential expression. Predominantly prostate cancer patients were examined, and the

differential probes isolated from metastatic cancer patients compared to normal patients were found to be diagnostic. One of ordinary skill in the art would not readily equate the results of metastatic breast cancer with that of very early stage breast cancer, given the fundamental differences between metastatic and non-metastatic cancers.

Further, Applicants note that in column 52 of Ralph *et al.*, it is asserted that in the early stages of the disease state, the immune response may be localized, that is, limited to lymph nodes immediately surrounding a metastasizing tumour or other localized form of a disease state. Thus, even if one of ordinary skill in the art were to contemplate using the method of Ralph *et al.* to determine early disease states, they would understand from Ralph *et al.* that lymphatic fluid should be examined. To the contrary, Applicants' claimed invention utilizes the analysis of blood.

Accordingly, the method of Ralph *et al.* is directed to the analysis of leukocytes having direct contact with the disease (tumor) cells in order to elicit an immune response in the leukocytes, which can then be detected. In view of this, it would be understood by one of ordinary skill in the art that the response would be localized to the lymph nodes and thus leukocytes within the lymph nodes should be examined. There is no indication that blood leukocytes which have not directly contacted early stage cancer cells could be used diagnostically. In this regard, Applicants note that Ralph *et al.* generates probes from blood samples from patients with metastatic cancer.

Further, Applicants respectfully submit that the Examiner's reliance on Ralph *et al.* is inapt since Ralph *et al.* is principally concerned with prostate cancer. In early stage prostate cancer, unlike breast cancer, the cancer cells are in direct contact with PBMCs; the prostate gland is well supplied with blood, the major blood supply to the prostate derives from the

branches of the internal iliac arteries that enter the gland with the major neurovascular pedicles at either superolateral aspect of the gland. For this reason, altered gene expression may be observable in blood cells in early stage prostate cancer by virtue of direct contact with cancer cells. However, breast cancer is distinct in this regard, as the early stages are confined to breast tissue, i.e, milk ducts, that does not come into contact with the blood. Nevertheless, Applicants again point out that Ralph *et al.* is concerned with metastatic cancer, wherein metastases typically traffic through the bloodstream and thus contact PBMCs.

In view of Ralph's understanding of the contact required between leukocytes and cancer cells to elicit detectable changes, one of ordinary skill in the art would have understood that early stage breast cancer cells, which do not contact blood cells, would not alter gene expression in blood cells that could be detected and used diagnostically. To the contrary, Ralph *et al.* only suggests that lymph node analysis is appropriate for examining early stage cancer.

Accordingly, the production of probes from breast cancer patients using PBMC from patients with very early stage breast cancer, or the diagnosis of such cancers using those probes, as is Applicants' claimed invention, is not rendered obvious by the cited references for the above reasons.

Withdrawal of the rejection is respectfully requested.

2. In paragraph 18 on page 7 of the Office Action, the Examiner rejects Claims 19 and 26-35 under 35 U.S.C. § 103 as being unpatentable over Ralph *et al.* in view of Lukas *et al.*, and further in view of Wadhwa *et al.*

Ralph *et al.* and Lukas *et al.* are relied upon as in the rejection of Claims 18 and 20-25, above.

The Examiner acknowledges that neither Ralph *et al.* nor Lukas *et al.* disclose a method wherein identified isolated nucleic acid markers are prepared on a solid support, namely a filter. In an attempt to rectify the deficiencies of the primary references, the Examiner relies upon Wadhwa *et al.*, who allegedly disclose a reverse Northern assay of DNA fragments isolated from differential display, and that this method has advantages over traditional Northern blots wherein the differentially displayed molecules were PCR amplified, bound to a membrane filter, and cDNA probes prepared from total RNA from cells. The Examiner concludes that it would have been obvious to substitute the Northern assays taught by Ralph *et al.* in view of Lukas *et al.* with the reverse Northern assays as taught by Wadhwa *et al.* to achieve the present invention.

Applicants respectfully disagree, and traverse the rejection on the following grounds.

Applicants note that the addition of Wadhwa *et al.* does not compensate for the deficiencies of Ralph *et al.* or Lukas *et al.*, as discussed above. Accordingly, Claims 19 and 26-35 are not rendered obvious by the cited references, at least for the reasons presented in the rejection of Claims 18 and 20-25 over Ralph *et al.* or Lukas *et al.*

Withdrawal of the rejection is respectfully requested.

Double Patenting

In paragraph 20 on page 2 of the Office Action, the Examiner provisionally rejects Claims 18-35 under the doctrine of obviousness-type double-patenting, as being unpatentable over Claims 1-36 of co-pending application Serial No. 11/149,370.

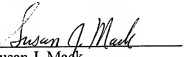
As this rejection is merely provisional in nature, Applicants respectfully request that the rejection be held in abeyance until such time as allowable subject matter is identified.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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